Bilateral simultaneous central retinal vein occlusion revealing Waldenström's macroglobulinemia

Occlusion bilatérale de la veine centrale de la rétine révélant la macroglobulinémie de Waldenström

Waldenström macroglobulinemia (WM) is defined by the World health organization (WHO) as a lymphoplasmacytic lymphoma associated with a monoclonal immunoglobulin M (Ig M) protein [1]. It is one of the malignant monoclonal gammapathies, characterized by the presence of high levels of Ig M, elevated serum viscosity and the presence of lymphoplasmacytic infiltrate in the bone marrow. Retinal symptoms are rare, the most common are retinal hemorrhages and retinal vein occlusion secondary to hyperviscosity, whereas serous macular detachment (SMD) and macular edema have occasionally been reported [2].

We report a rare case of WM revealed by bilateral simultaneous central retinal vein occlusion (CRVO) with macular edema and SMD.

A 60-year-old man presented to our department complaining of bilateral blurred vision since two weeks associated with asthenia and vertigo. He had a history of poorly controlled hypertension and he was a heavy smoker with 25 packs year. His best corrected visual acuity (BCVA) was 20/40 P4 in both eyes. Anterior segment examination was unremarkable and intraocular pressure was normal. Fundus examination (FE) of both eyes revealed retinal hemorrhages in all quadrants, peripheral microaneurysms, dilation and tortuosity in retinal veins suggesting a hyperviscosity syndrome (figure 1). Bilateral and simultaneous CRVO was diagnosed and confirmed by fluorescein angiography (FAG) (figure 1). Spectral-domain optical coherence tomography (SD-OCT) showed bilaterally extensive cystoid macular edema with SMD (figure 1). General medical examination revealed blood pressure at 130/70, bilateral ear-buzzing and, cutaneous and mucosal pallor. Physical examination didn’t find hepatomegaly, splenomegaly or lymphadenopathy. Neurological examination revealed only paresthesia. There was no confusion or memory impairment. Blood investigations showed anemia of 5.9 g/dL, leucocytosis of 6280/mm³, and hyperprotidemia of 127.3 g/L. Electrophoresis of proteins showed gammaglobulinemia of 56.3 g/L (figure 2). Immunofixation electrophoresis revealed monoclonal gammapathy of Ig M, kappa type (2.8 g/L), which was also identified in urine. A massive proliferation of lymphocytes (76%) was found in sternal bone marrow puncture, many of them were lymphoplasmacytic. The diagnosis of WM was made. The patient was treated by plasmapheresis and chemotherapy sessions using the protocol RCD (rituximab, cyclophosphamide, and dexamethasone).

Two months after the systemic therapy (five sessions of plasmapheresis and three sessions of chemotherapy), general health status of the patient became better, visual acuity improved to 20/25 P2 in both eyes. FE revealed almost complete resolution of retinal hemorrhages in the right eye and their marked regression in the left eye (figure 3). SD-OCT showed reduction of central macular thickness but persistence of SMD (figure 3).

Six months after the systemic therapy (six sessions of plasmapheresis and six sessions of chemotherapy), visual acuity improved to 20/20 P2 in both eyes. FE revealed bilateral almost complete resolution of hemorrhages (figure 4). SD-OCT showed in both eyes disappearance of SMD, good foveal depression but persistent of perifoveal cystoid spaces (figure 4).

Discussion

Bilateral CRVO is a rare presenting feature of WM, secondary to serum hyperviscosity, which affects 15% to 30% of all patients with WM [3–5]. Although rare, it is a known complication usually associated to poor visual prognosis. The most common retinal findings include scattered retinal hemorrhages and microaneurysms, vascular dilation and tortuosity, venous beading, and optic disc edema [6,7]. At the time of diagnosis, approximately 8% of patients with WM report visual disturbance [5].

Glossary

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<th>Acronym</th>
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<td>WM</td>
<td>Waldenström macroglobulinemia</td>
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<td>Ig M</td>
<td>immunoglobulin M</td>
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<td>SMD</td>
<td>serous macular detachment</td>
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<td>CRVO</td>
<td>central retinal vein occlusion</td>
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<td>BCVE</td>
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<td>RCD</td>
<td>rituximab – cyclophosphamide – dexamethasone</td>
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<td>VEGF</td>
<td>vascular endothelial growth factor</td>
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Macular edema secondary to CRVO is frequently associated with SMD [8]. Nevertheless, SMD in the WM disease is rare. The proposed physiopathology is the accumulation of Ig M in the subretinal space through discontinuity of the outer retinal layers, causing therefore an increase in the osmotic gradient and consequently a fluid accumulation under the retina [7]. This pathogenesis is different from that of the SMD observed in other pathologies such as exudative age-related macular degeneration or diabetic macular edema and it explains the lack of leakage or “silent macula” seen on FAG which is a characteristic of immunogammopathy-induced serous macular detachment [2].

Treatment of SMD in patients with WM is challenging. Treatment guidelines are lacking as this entity is rare and management methods are based on reviews of case reports and clinical judgments. Nevertheless, plasmapheresis seems to be necessary. Fenicia et al. [9] reported a case treated with intravitreal dexamethasone implant without systemic therapy for WM. The patient achieved partial anatomical resolution with no improvement in the final visual acuity. The authors concluded that plasmapheresis is needed to improve the effectiveness of the treatment. Plasmapheresis in WM patients leads to a reduction of serum viscosity and Ig M’s level, with an improvement of retinopathy and normalization of retinal hemodynamics as evidenced by a reduction of the diameter of the retinal veins [3,10]. Since the SMD is presumed to be secondary to the accumulation of Ig M, plasmapheresis is therefore necessary to decrease Ig M’s level. Our patient was treated only by systemic therapy with improvement of ocular and systemic symptoms.
Although systemic treatment can improve the macular detachment and grant a mild visual gain, many patients have persistent subretinal fluid and a poor functional prognosis. Baker et al. [7] reported that in two patients treated exclusively by plasmapheresis and chemotherapy, intra-retinal edema and neurosensory detachment completely resolved in only one patient after 5 months of treatment. For Alexander et al. [3], only two of their three patients treated with plasma exchange followed by systemic chemotherapy had a significant visual improvement. Therefore, given the poor response of SMD in patients with WM, other therapeutic options have been tried to manage this condition. Fenicia et al. [9] had not reported the efficacy of treatment with dexamethasone implant in WM. However, in that case, no systemic therapy for WM was initiated. For intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF), Xu et al. [6] demonstrated that bevacizumab induces significant reduction in intra-retinal fluid, but minimal change in persistent subretinal fluid and final vision. Ratanam et al. [11] tried concomitant treatment by plasmapheresis and repeated injections of bevacizumab. They reported a partial anatomical resolution but a significant improvement in visual acuity. They suggested that early therapy with anti-VEGF can protect the retina from the effects of hypoxia caused by retinal non-perfusion, improve the macular edema and participate in the regulation of inflammatory factors. Besirli and Johnson [12] have tried the conventional treatment of macular edema, including repeated injections of bevacizumab, panretinal photocoagulation and intravitreal corticosteroids in a patient initially treated with systemic therapy and in whom macular detachment and edema persisted after 4 months of treatment. They did not report any additional benefit and concluded that in case of systemic immunogammopathy, conventional treatments for macular edema are ineffective and that the best treatment remains etiologic in spite of a slow and incomplete response.

In conclusion, bilateral CRVO is rarely identified as a presenting feature in WM. Early systemic plasmapheresis is a cornerstone in the treatment of immunogammopathy-induced maculopathy by reducing Ig M level. However, it is unknown how long Ig M can persist in the subretinal space. Therefore, it would be better to start with a systemic treatment alone. Further research is needed to evaluate the efficacy of intravitreal injections of anti-VEGF in this condition. However, they can be proposed in cases of poor response.
Two months after systemic chemotherapy and plasmapheresis. CF photographs demonstrated significant regression of retinal hemorrhages, decrease venous dilation and tortuosity in both eyes (a and b). SD-OCT demonstrated reduction of central macular thickness but persistence of serous macular detachment in RE (c) and LE (d).
Six months after systemic chemotherapy and plasmapheresis. CF photograph demonstrated almost complete resolution of retinal hemorrhages in both eyes (a and b). FAG demonstrated no significant macular angiographic leakage in both eyes (c and d). SD-OCT demonstrated disappearance of serous macular detachment and persistence of perifoveal intra-retinal cystoid spaces (e and f).
Letter to the editor

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References


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